

**REMARKS**

**Status of Claims and Amendment**

Upon entry of this amendment, which is respectfully requested, claims 1, 4, 9, 18, 37, and 45 will be amended. Claims 4-6 are canceled. Claims 1-4, 7-15, and 16-52 are all the pending claims in this application. Claims 1-52 are rejected. Claims 1, 9 and 45 are objected to.

Claim 1 has been amended to include the recitations “wherein the indole derivative in reaction step 1 is not substituted at the 3-position”, and “indole derivative” at reaction step 1. Support for the amendments to claim 1 may be found throughout the specification, for instance, at page 7, line 17 to page 8, 1<sup>st</sup> and 2<sup>nd</sup> paragraph, and claims 4 and 5.

Claim 9 has been amended to include the recitation “a mixed solvent of aprotic solvent and C<sub>1-3</sub> alcohol solvent”. Support for the amendments to claim 9 may be found throughout the specification, for instance, support for the amendments to claim is implicitly disclosed at page 13, 1<sup>st</sup> paragraph.

Claim 18 has been amended to include the recitation “selected from the group consisting of formalin, paraformaldehyde and trioxane.” Support for the amendments to claim 18 may be found throughout the specification, for instance, at page 7, lines 20-23.

Claim 24 has been amended to include the recitation “+ an indole derivative”. Support for the amendment to claim 24 may be found throughout the specification, for instance, at page 7, 7<sup>th</sup> full paragraph.

Claim 37 has been amended to include the recitation “R<sup>1</sup> is hydrogen and R<sup>2</sup> is a protecting group for an amino group, or R<sup>1</sup> is a protecting group for an amino group and R<sup>2</sup> is hydrogen”. Support for the amendments to claim 18 may be found throughout the specification, for instance, at page 3, 2<sup>nd</sup> full paragraph.

Claim 45 has been amended to be amended to be more in conformance with idiomatic English and standard PTO practice.

Support for new claim 53 may be found throughout the specification and claims 1 and 6.

Support for new claims 54-55 may be found throughout the specification and claims 2 and 3.

Support for new claims 56-57 may be found throughout the specification and claims 6 and 7.

No new matter is added.

#### **Claim to Priority**

Applicants thank the Examiner for acknowledgement of the claim to priority to Japanese Application No. 2003-349318 filed October 8, 2003, Japanese Application No. 2003-350441 filed October 9, 2003, and Japanese Application No. 2003-350439 filed October 9, 2003, as well as receipt of the certified copies of the priority documents.

#### **Information Disclosure Statements**

Applicants thank the Examiner for acknowledgement of the Information Disclosure Statements filed April 5, 2006, July 25, 2006, and September 3, 2004, by returning initialed copies of the PTO Forms SB/08 submitted therewith.

**Response To Claim Rejections Under 35 U.S.C. § 102(b)**

On page 2 of the Office Action, the Office Action rejects claims 1-5, 7-14 and 32-44 under 35 U.S.C. § 102(b), as being anticipated by Shiota et al. (European Patent Application Publication No. 1 179341-A1) (hereafter “Shiota”).

1. The Office Action alleges that Shiota anticipates reaction step 1 of instant claim 1. Specifically, the Office Action alleges that at pages 218 (line 55) - 219 (line 50), Shiota disclose reaction step 1 for the synthesis of compounds 2235 and 2241 (described on page 215 of Shiota). The Office Action contends that compounds 2235 and 2241 are encompassed by formula (I) as recited in instant claim 1. Moreover, although the Office Action acknowledges that Shiota fails to specifically disclose the use of a “synthon of formaldehyde,” such as formalin, in combination with indole (claims 4 and 5), the Office Action asserts that “synthon” by definition is a synthetic equivalent, and thus can be interpreted as “anything equivalent to formaldehyde.” Accordingly, the Office Action concludes that “preparation process 3” on page 219 of Shiota is a process equivalent to the use of a synthon of formaldehyde, as recited in instant claim 4.

The Office Action also appears to suggest that Shiota discloses reaction step 2 of instant claim 1. In this regard, the Office Action alleges that Shiota discloses the protection of reactive functional groups such as amines (page 221, lines 1-17) using t-butoxycarbonyl (reference example 1, page 221, line 26), and the removal of such protective groups using HCl in organic solvent (page 246, example 749).

Applicants respectfully submit that Shiota does not explicitly or inherently disclose the claimed method for producing aminopyrrolidine derivatives of formula (I).

Applicants note that the indole derivatives disclosed by Shiota to which the Office Action refers (compounds 2235 and 2241, page 215) all contain a CH<sub>2</sub> group at the 3-position. However, the presently claimed invention mandates that “reaction step 1 is [a] reaction of an indole derivative having no substituent at the 3-position in the presence of a synthon of formaldehyde” (emphasis added). Even if the Examiner’s interpretation of “synthon” were correct, which Applicants contest, Shiota fails to disclose a reaction containing an indole derivative having no substituent at the 3-position in the presence of a synthon of formaldehyde.

Claims 4-6 are canceled.

With regard to claims 7 and 8, Applicants note that Shiota does not disclose removal of a protecting group via acid hydrolysis or treatment with HCl in organic solvent with regard to compounds of the structure recited in instant claim 1.

Furthermore, new claims 53-57 are not anticipated by Shiota because Shiota does not explicitly or inherently disclose the claimed reaction of an indole derivative having a dialkylaminoethyl group at the 3-position.

Thus, Shiota fails to teach each and every limitation of the claimed invention, as is required to maintain a rejection under 35 U.S.C. § 102(b).

**Accordingly, reconsideration and withdrawal of the rejection under §102(b) is respectfully requested.**

2. With regard to claims 9-14, the Office Action suggests that Shiota discloses the method of instant claim 9 on pages 219-220, under “preparation process 4.” Specifically, the Office Action alleges that Shiota discloses the use of the condensing agent DCC (1,3-dicyclohexylcarbodiimide) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (page 218, line

45). Further, the Office Action alleges that Shiota discloses the use of the additive 1-hydroxy-1,2,3benzotriazole (HOBt) in the same reaction in addition to the use of triethylamine on page 218.

Applicants respectfully submit that Shiota does not disclose the presently claimed method for producing aminiopyrrolidine derivatives or salts thereof comprising a condensation step represented by the reaction formula (II), wherein the condensation step is performed by treatment with an anthranilic acid derivative in a mixed solvent of aprotic solvent and C<sub>1-3</sub> alcohol in the presence of a condensing agent.

**Accordingly, reconsideration and withdrawal of the rejection under §102(b) is respectfully requested.**

3. With regard to claims 37-44, the Office Action alleges that at page 218, Shiota discloses compounds of formula III which anticipate the compounds of instant claims 37-44 when taken with the selection of the variables for the two species of compounds 2235 and 2241.

Applicants respectfully submit that Shiota does not explicitly or inherently disclose the presently claimed compound or salt thereof represented by formula (III) wherein R<sub>1</sub> is a protecting group for an amino group. Applicants note that Shiota fails to disclose the use of protecting groups with regard to the presently claimed compounds of the present invention.

Thus, because Shiota does not disclose the use of protecting groups with the presently claimed compounds, Shiota fails to teach each and every limitation of the claims. Shiota does not anticipate the claimed invention.

**Accordingly, reconsideration and withdrawal of the rejection under §102(b) is respectfully requested.**

**Claim Rejections under 35 U.S.C. § 103(a)**

On page 5 of the Office Action, the Office Action rejects claims 1-52 under 35 USC §103(a) as being unpatentable over Shiota in view of Katritzky et al. (J. Org. Chem. 1990, v55, p3688-3691) (hereafter “Katritzky”) and Schelhaas et al. (Angew. Chem. Int. Ed., 1996, v35, p2056-2083) (hereafter “Schelhaas”).

The Office Action alleges that Shiota discloses methods for producing compounds which anticipate the genus of the instantly claimed methods. Further, the Office Action alleges that Katritzky discloses the use of dialkylaminomethyl as a protecting group on indole, and Schelhaas discloses general protecting group strategies and steps to optimize the production of a desired product having reactive groups such as amines and amides in the final product.

1. The Office Action alleges that Shiota discloses all the elements of claim 6, but does not specifically disclose a dialkylaminomethyl protecting group on an indole. In view of this, the Office Action alleges that Katritzky discloses the use of dialkylaminomethoyl protecting groups for substituted indole synthesis, including N,N-dimethylaminomethyl-indole, gramine and isogramine. The Office Action asserts that the chemistry of indoles and the use of protecting groups are well known in the art and thus if one of ordinary skill in the art were to attempt to synthesize the compounds of the claimed method, they would have a reasonable expectation of success of arriving at the claimed invention by combining these references.

Claim 6 is canceled.

With regard to new claims 53-57, Applicants respectfully submit that it would not have been obvious for one of ordinary skill in the art to combine Shiota and Katritzky to obtain the claimed invention.

Initially, Applicants submit that “if the prior art merely discloses compounds as intermediates [without utility] in the production of a final product, one of ordinary skill in the art would not have been motivated to stop the reference synthesis and investigate the intermediate compounds with an expectation of arriving at claimed compounds which have different uses.” M.P.E.P. §2144.09.

In this case, Applicants note that the dialkylaminomethyl group of the present invention is used to form part of the resulting skeleton of the claimed compound. In contrast, and as acknowledged by the Office Action, Katritzky discloses the use of dialkylaminomethyl as a protecting group. The technical concept to utilize dialkylaminomethyl group in the present invention is different from that in Katritzky, and would not motivate an ordinary artisan to use dialkylaminomethyl group on indole group as claimed. Specifically, the indole synthesis described in Katritzky does not use dialkylaminoethyl to form part of the resulting skeleton as in the claimed method, but rather, uses it as a protecting group, there is no reason or motivation for one of ordinary skill in the art to modify the method of Shiota with the teachings of Katritzky and obtain the claimed method.

**Accordingly, reconsideration and withdrawal of the rejection under §103(a) is respectfully requested.**

2. The Office Action asserts that the processes of claims 15 and 16 differ from that disclosed by Shiota only with regard to specific recitation of the amine deprotection step

described in “reaction step 4.” However, the Office Action alleges that Schelhaas discloses the use of acid-labile protecting groups as “one of the best established methods in protecting group chemistry”, and therefore, one of ordinary skill in the art would have been motivated to use protecting group chemistry to protect the reactive amine and subsequent deprotection by acid hydrolysis with HCl in an organic solvent, as is disclosed by Schelhaas.

In response, Applicants respectfully submit that Shiota does not disclose the presently claimed production method further comprising a deprotection step represented by reaction step 4.

Furthermore, because Katritzky and Schelhaas does not cure the deficiencies of Shiota, as discussed in the response to the §102(b) rejection, the present claims are not *prima facie* obvious over Shiota combination with either Katritzky or Schelhaas.

Specifically, Applicants disagree with the Office Action, and submit that one of ordinary skill in the art would have no reason to introduce protecting group chemistry, as disclosed by Schelhaas, into the methods of Shiota because Schelhaas clearly states on page 2078, column 2, lines 8-9, that “[t]he best protecting group is no protecting group” (emphasis added). Further, Schelhaas concludes that “an unavoidable consequence of the introduction and removal of protecting groups is that the synthesis is lengthened, and that the use of protective groups is thus often seen as unproductive.” Thus, one of skill in the art would understand from Shiota that the reaction can be performed without the need for protecting groups, and from Schelhaas that it is preferable not to use protecting groups if the reaction can be performed without them. Thus, Schelhaas teaches away from introducing protection groups into a reaction that can be performed in their absence.



Also, as acknowledged by the Examiner, Shiota differs from the claimed invention because Shiota does not disclose the claimed amine deprotection step of reaction step 4. (See last paragraph on page 6 of Office Action).

Applicants note that Example 21 of the specification discloses a mixed solvent of ethyl acetate and methanol is used for the claimed reaction. In this regard, tetrahydrofuran and ethyl acetate are aprotic solvents and methanol is C<sub>1</sub> alcohol and 2-propanol is C<sub>3</sub> alcohol.

In case a co-solvent such as methanol is not applied, the undissolved material is hard to suspend, and becomes a crucial obstruction to the reaction when the reaction is performed on an industrial scale. The Rule 1.132 Declaration by Takeyasu, submitted herewith shows only reaction step 5 was performed.

Although the Office Action asserts that the combination of EtOAc and MeOH is better than that of THF and MeOH because evaporation prior to sodium hydroxide washing is not needed, both are preferable in terms of industrial applicability as mentioned above compared to aprotic solvent such as THF or EtOAc only, or C<sub>1-3</sub> alcohol only. Also, in the case when excess of MeOH is used together with aprotic solvent such as EtOAc, both yield and purity decrease.

**Accordingly, reconsideration and withdrawal of the rejection of claim 16 under §103(a) is respectfully requested.**

3. The Office Action rejects claims 17-20, 24-31 and 45-52 as being obvious over Shiota. The Office Action alleges that coupling reactions similar to those claimed by applicant are disclosed by Shiota, but that one of ordinary skill in the art would be motivated to modify the methods disclosed by Shiota to start with cheaper and simpler starting materials.

Applicants submit that the presently claimed invention is not obvious over Shiota for at least the following reasons.

The deficiencies of Shiota are discussed in the response to the §102(b) rejection. Hence, the present claims are not *prima facie* obvious over Shiota.

Furthermore, Applicants note that the Office Action has failed to provide any evidence to show that the starting compounds disclosed by Applicants would be less expensive, nor does the Office Action suggest why starting with a “simpler” starting material would be advantageous. Conversely, one of ordinary skill in the art would recognize that starting with “simpler” reactants would inherently require more reaction steps to achieve the final product, which would likely have detrimental effects on yield and purity and would be more time consuming.

As discussed above, and shown in the Rule 1.132 Declaration by Takeyasu, when a co-solvent such as methanol is not applied, the undissolved material is hard to suspend, and obstructs the reaction when the reaction is performed on an industrial scale. Also, the combinations of EtOAc and MeOH, and THF and MeOH are preferred as mentioned above for industrial application as compared to aprotic solvent such as THF or EtOAc only, or C<sub>1-3</sub> alcohol only. Moreover, both yield and purity decrease when excess of MeOH is used together with an aprotic solvent such as EtOAc.

Thus, claims 17-20, 24-31 and 45-52 are not obvious.

**Accordingly, reconsideration and withdrawal of the rejection under §103(a) is respectfully requested.**

4. With regard to claims 21-23, the Office Action alleges that one of ordinary skill in the art would have been motivated to adopt the methods of protection group chemistry disclosed

by Shiota to protect the reactive amine. Further, the Office Action asserts that one of ordinary skill in the art would have selected a benzyl protecting group, and its removal with hydrogen and a palladium catalyst, as disclosed by Schelhaas, when confronted with the challenge of the stepwise synthesis of the product disclosed by Schelhaas.

The deficiencies of Shiota and Schelhaas are discussed above. In addition, Applicants submit that, from the methods disclosed by Schelhaas and Shiota, one of ordinary skill in the art would have chosen a benzyl protecting group to protect the reactive amine. As mentioned above, Schelhaas teaches away from introducing protection groups into a reaction that can be performed in their absence. Further, Schelhaas does not disclose that a palladium catalyst and hydrogen can be used to remove a benzyl protective group. Rather, Schelhaas only discloses that a palladium catalyst is useful for the removal of protecting groups containing an allyl group.

Thus, one of ordinary skill in the art would not arrive at the claimed invention by following the methods of Shiota and Schelhaas. Accordingly, the cited references do not render the claims obvious.

**Accordingly, reconsideration and withdrawal of the rejection under §103(a) is respectfully requested.**

### **Response To Claim Rejections under 35 U.S.C. § 112**

On page 8 of the Office Action, the Office Action rejects claims 4, 5, 18 and 19 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action asserts that recitation of “synthon of formaldehyde” can be construed as encompassing a huge number of possible definitions in a given synthetic process and that the instant specification provides no guidance as to the boundaries of the scope of the

claims. The Office Action concludes that there is no written description suggesting that the applicant actually had possession of the claimed invention beyond the one example provided (i.e. formalin).

Applicants submit that that teachings of the specification when combined with the knowledge of one of ordinary skill in the art are sufficient to comply with the written description requirement. A person of ordinary skill in the art would understand from reading the specification, for instance, at page 7, lines 20-23, that the synthon of formaldehyde is selected from the group consisting of formalin, paraformaldehyde and trioxane.

**Accordingly, reconsideration and withdrawal of the rejection under §112 is respectfully requested.**

#### **Response To Claim Objections**

On page 9 of the Office Action, the Office Action objects to claims 1, 9, and 45 as allegedly having unclear language in reference to the preamble and the inclusion of a chemical formula. The Office Action recommends rephrasing the preamble of the relevant claims to recite “A method of producing aminopyrrolidine derivatives of formula (I) or salts thereof comprising reaction steps 1 and 2...”

In response, Applicants have amended the claims as suggested by the Office Action to even further clarify the claimed invention.

**Accordingly, withdrawal of the grounds of objection is respectfully requested.**

**CONCLUSION**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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CUSTOMER NUMBER

Date: October 29, 2007